REMARKS/ARGUMENTS

Claims 10-12 and 14 are pending herein.

Examiners Westerberg and Silverman are thanked for discussing the case with Applicants' representatives on October 30, 2008. Claim 10 has been amended based upon the joint discussion at that time. More particularly, the phrase "in a human being" has been inserted after "treating" in line 1. The affliction treated is also restricted to diffuse macular edema. Claim 13 has been cancelled and claims 11 and 12 have been amended to be commensurate with the changes to claim 10. The claims are patentable for the reasons discussed during the interview and indicated below.

The rejection of all pending claims under §103(a) as unpatentable over Akita et al. in view of Lopes de Faria et al., if applied to the claims as amended, is respectfully traversed.

As part of the Examiner's support of the rejection, it was asserted that the claims finally rejected were directed to treatment of mammals, which was a term broad enough to include rats. The claims have been changed to restrict the treatment to humans and, moreover, the claims have been further amended to call specifically for the treatment of diffuse macular edema in diabetic maculopathy, again a change to address comments appearing in the Final Rejection directed to the breadth of the claims versus the treatments discussed and shown in the specification, Arguments, and Declaration filed July 16, 2008.

Applicants again emphasize that the primary reference describes a treatment method for diabetic retinopathy and not diabetic maculopathy. The Akita et al. tests were for the former, which did not require an increase in intraocular pressure. Tests for the latter did so require. Examiners Westerberg and Silverman asked that the record establish or show how or why there are differences between the two treatments.

Examiners Westerberg and Silverman are directed to the specification, more particularly, the paragraph bridging pages 1 and 2 of the specification, which contains a discussion of the differences between diabetic maculopathy (DM) and diabetic retinopathy (DR). The latter is intended to be treated to prevent blindness (loss of visual acuity) while diabetic maculopathy treatment is to prevent and ameliorate deterioration of visual acuity. As noted in the remarks in the last response and during the interview, Akita et al. teaches the use of SNK-860 for the treatment of diabetic retinopathy, not diabetic maculopathy. Moreover, the tests shown in Akita et al. establish that the material is useful in experimental tests in animals, but there is no evidence in that reference of any treatment or indeed any success in clinical treatment using that compound in the treatment of DR. Indeed, to date, there are no results showing the successful use of SNK-860 in clinical trials in treating DR. Applicants, again, respectfully submit that there is no reason for a person of ordinary skill in the art, taking into consideration the evidence of record in which SNK-860 is unable successfully to clinically treat DR, to have any expectation that the material would be successful clinically in the treatment of humans for DM. The clinical trial of SNK-860 in humans in treating DM is shown in Test Example 4 in the specification; Examiners Westerberg and Silverman are directed to the specification at page 15 and continuing to the end.

Examiners Westerberg and Silverman had requested further explanation that SNK-860 was not effective in clinical trials for DR. Applicants direct the Examiner to Thomas A. Ciulla et al., *Diabetic Retinopathy and Diabetic Macular Edema*, **Diabetes Care**, Volume 26, Number 9, September 2003, pages 2653-2664; Matthew A. Speicher et al., *Pharmacologic Therapy for Diabetic Retinopathy*, **Expert Opinion on Emerging Drugs**, Volume 8, No. 1, 2003, pages 239-250; and N. Hotta et al., *Diabetic Retinopathy- Experimental and Clinical Approaches from Polyol Pathway*,

Current Concepts of Aldose Reductase and its Inhibitions, Amsterdam: Elsevier Science Publishers B.V., 1990, pages 169-177. Copies of these publications are enclosed.*

The Ciulla reference, from the last phrase on page 2657 to the first paragraph on page 2658, discloses that ARIs did not work well in clinical trials. Three ARIs were exemplified, i.e., sorbinil, ponalrestat, and tolrestat. Tolrestat was not effective for DR. Sorbinil and ponalrestat were partially effective, but practically ineffective. In addition, the first paragraph on page 2658 discloses that inhibition of the aldose reductase pathway alone is insufficient to impact diabetic microvascular complications.

The first paragraph on page 242 of the Speicher reference discloses that ARIs have been under intense clinical study for diabetic complications, without consistent benefit.

The Hotta reference discloses that epalrestat was effective in clinical trials for DR.

From these references, one can see that (i) only epalrestat is effective for DR, (ii) sorbinil, ponalrestat, and tolrestat are not effective for DR, and (iii) ARIs are hardly effective in clinical trials for DR and other diabetic complications.

Based on these references, one can easily establish by analogy that SNK-860 would not be effective in clinical trials for DR. Generally speaking, if a medicine is not effective for a particular disease, the resulting negative data will not be disclosed in academic documents. The data of sorbinil, ponalrestat, and tolrestat for DR was disclosed because partial efficacy was obtained by sorbinil or ponalrestat treatment.

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* The Hotta reference was also attached to the Amendment filed July 16, 2008, and the Speicher reference was also cited in the Information Disclosure Statement filed December 17, 2007.

In addition, attached is a portion, with translation, of an investigational brochure for SNK-860 that was filed with the Health, Labour and Welfare Ministry in Japan as proof that SNK-860 was not effective in clinical trials for DR.

During the interview, Examiners Westerberg and Silverman had also asked about the significance of the tests reported in the Declaration Under 37 C.F.R. 1.132 filed July 16, 2008. The test reports there were to affect a comparison between SNK-860 and epalrestat, a compound that was the only one among aldose reductase inhibitors (ARI) that had been shown to be capable of giving positive effects on DR in both animal experiments and human clinical trials. Thus, the epalrestat was used as a control for comparison with SNK-860 in crab-eating monkeys having experimental diabetes. The results reported in that Declaration show that SNK-860 was much more effective in treating diffuse macular edema in diabetes mellitus than epalrestat. The experimental techniques and models used in the Declaration and specification were chosen because macula lutea is a special retinal site having an outer retinal layer such as a visual cell layer and does not have an inner layer. Macula lutea is found in primates, but is not found in rats. Thus, the Test Examples 1 and 2 in the specification in rats showed examinations of diffuse retina edema by the thickness of visual cell layer and damage of the ganglian cells by the degree of loss of nuclei. The latter test shows that SNK-860 has potency on retinal (macular) function leading to a visual acuity. In the monkey model, an experimental model of diabetic maculopathy was done by forming diffuse macular edema in the macula lutea of diabetic monkeys because, as indicated above, monkeys possess macula lutea, as do humans. As such, the results clearly establish the unexpected-in-the-art results accomplished by the present invention, and the rejection should be withdrawn.

If Examiner Westerberg believes that contact with Applicants' attorney would be advantageous toward the disposition of this case, she is herein requested to call Applicants' attorney at the phone number noted below.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 50-1446.

Respectfully submitted,

December 11, 2008
Date

Stephen P. Burr
Reg. No. 32,970

SPB/CW/tlp

Attachments:

Ciulla reference
Speicher reference
Hotta reference
Portion of Investigational Brochure for SNK-860 (w/ English translation)

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